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(54) Title: A PHARMACEUTICAL FORMULATION OF BALAGLITAZONE

(57) Abstract: A formulation of 5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione and/or pharmaceutically acceptable salts thereof is provided.

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A PHARMACEUTICAL FORMULATION OF BALAGLITAZONE

FIELD OF THE INVENTION

The present invention relates to solid pharmaceutical formulations of 5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione and pharmaceutical acceptable salts thereof.

BACKGROUND OF THE INVENTION

5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione and pharmaceutically acceptable salts thereof have been found useful in the treatment of type 2 diabetes acting as a insulin sensitizer as disclosed in WO 97/41097.

The active ingredient is present as the base or as a pharmaceutically acceptable salt, preferably as the potassium salt.

Various solutions have been proposed for the formulation of 5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione.

WO 97/04197 discloses particular formulations comprising lactose, cornstarch, carboxymethyl cellulose and magnesium stearate; or calcium phosphate, lactose, cornstarch, PVP and magnesium stearate. Tablets are made by granulation followed by compression.

WO 00/32191, WO 01/91751 and WO 01/89523 disclose that 5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione may decompose in the presence of water and air, and that an improved stability is achieved by making low water content formulations. In particular, formulations comprising anhydrous lactose, microcrystalline cellulose and magnesium stearate are disclosed.

WO 02/72069 discloses that improved homogeneity may be achieved in low dose tablets comprising less than 3% of 5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione by means of microcrystalline cellulose and silicium dioxide.

The low water content of some of the formulations suggested in, e.g., WO 00/32191 impose a restriction on what excipients can be used, and the formulation suggested in WO 02/72069 is only relevant for low dose formulations. The tablets disclosed in WO 97/04197 are made in a process that requires at least two major process

steps, i.e., granulation and compression. It would be advantageous to have a process where granulation is not necessary so that only one major process step, i.e., compression, is required.

Formulations with higher amounts of 5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione are difficult to make owing to flowability issuesand mixing properties caused by the increased amount of the active ingredient, which makes the manufacture of tablets by direct compression difficult.

The present Invention provides a pharmaceutical formulation comprising more than 3% of 5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione, and wherein the excipients need not have a low water content. The formulation disclosed herein can be prepared by direct compression.

SUMMARY OF THE INVENTION

In one embodiment, the invention provides a solid pharmaceutical composition comprising:

Component	Amount
5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione or pharmaceutically acceptable salt thereof	3.1 — 15 %
Lactose	44 - 88%
Silicified microcrystalline cellulose	5 - 44%
Magnesium stearate	0.5 — 2%
Talc	0.5 — 3%

In another embodiment, the invention provides a mixture comprising:

Component	Amount
5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione or pharmaceutically acceptable salt thereof	3.1 — 15 %
Lactose	44 - 88%
Silicified microcrystalline cellulose	5 - 44%
Magnesium stearate	0.5 — 2%
Talc	0.5 — 3%

In another embodiment, the invention provides a process for the preparation of a pharmaceutical composition, the method comprising the steps of forming the above mixture.

DESCRIPTION OF EMBODIMENTS

To describe the invention, certain terms are defined herein as follows.

Unless stated differently, all amounts stated in % is intended to indicate % (w/w) with respect to the total weight of the composition.

In the present context, a mixture is intended to indicate an essentially dry composition comprising two or more components, which components are themselves essentially dry.

In the present context, the term "solid pharmaceutical composition" is intended to indicate any pharmaceutical composition which appears essentially dry. Examples include tablets, troches, dragees, pills, lozenges, powders, granules and hard and soft capsules comprising powder. Particular mentioning is made of tablets.

The term "about" is defined as plus/minus 5% of the value of the stated amount.

Pharmaceutically acceptable salts forming part of this invention include salts such as alkali metal salts like Li, Na, and K salts, alkaline earth metal salts like Ca and Mg salts, salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline and the like, ammonium or substituted ammonium salts, aluminium salts. Salts may include acid addition salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, succinates, palmoates, methanesulplionates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates. Particular mentioning is made of the potassium salt.

In one embodiment, the pharmaceutical composition or the mixture of the present invention comprise 5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof in an amount of 5 — 12%, such as 8 — 11%, such as around 10%.

In one embodiment, the pharmaceutical composition or the mixture of the present invention comprise lactose in an amount of 50 — 75%, such as 60 — 70%, such as around 68%.

In one embodiment, the pharmaceutical composition or the mixture of the present invention comprise silicified microcrystalline cellulose in an amount of 5 — 40%, such as 10-30%, such as 15 — 25%, such as around 20%. In one embodiment, the pharmaceutical composition or the mixture of the present invention comprises 20-44% silicified microcrystalline cellulose.

In one embodiment, the pharmaceutical composition or the mixture of the present invention comprise magnesium stearate in an amount of 0.5 -1%, such as around 0.75%.

In on embodiment, the pharmaceutical composition or the mixture of the present invention comprise talc in an amount of 1 - 2%, such as around 1.5%.

In one embodiment, the invention relates to pharmaceutical compositions or mixtures comprising the potassium salt of 5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl)-thiazolidine-2,4-dione.

In one embodiment, the pharmaceutical composition of the present invention is a tablet, a capsule or a powder, and in particular a tablet.

Lactose is used as a filler and various lactose grades are commercially available with different physical properties, such as particle size distribution, water content and flow-ability properties. Examples of lactose suitable for the present invention include α- and β-lactose either as monohydrate or in the anhydrous form. Particular mentioning is made of lactose qualities for direct compression, i.e., lactose qualities with a low content of small particles or fines. Examples of such qualities include lactose with <63 μm NTM 20%, such as <63 μm NMT 16%, such as <63 μm NMT 6%; or <45 μm NTM 20%, such as <45 μm NMT 15%, such as <45 μm NMT 6%; or <32 μm NMT 10%. "<63 μm NMT 20%" indicates that Not More Than 20% of the particles have a diameter below 63 μm.

In one embodiment, lactose is agglomerated a-lactose monohydrate.

Tabletose 70 is one trade name for a lactose suitable for the present invention.

Silicified microcrystalline cellulose is prepared by co-processing microcrystalline cellulose and typically up to 5% colloidal silicon dioxide. Particular mentioning is made of silicified microcrystalline cellulose comprising 2% colloidal silicon dioxide. Silicified microcrystalline cellulose is used as a filler in order to improve compaction properties. several qualities of silicified microcrystalline cellulose can be used in the present invention, and in particular a quality suited for direct compression, such as a grade with a median particle size around 90 μm.

ProSolve HD 90 is one trade name for silicified microcrystalline cellulose suitable for the present invention.

Magnsium stearate is used a lubricant and any grad can be used. Talc is used a glidant and any grade can be used.

Particular mentioning is made of a pharmaceutical composition, in particular a tablet, or a mixture comprising:

Component	Amount
5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyll-thiazolidine-2,4-dione, potassium salt	9.96 %
a-Lactose monohydrate	67.79%
Silicified microcrystalline cellulose (2% SiO_2)	20.0%
Magnesium stearate	0.75%
Talc	1.5%

In the present context, flowability is understood to be the ability of a mixture to flow. Flowability of a mixture is a function of its particle shape and size distribution of the components of the mixture. Flowability may be important, e.g., due to a great impact on the quality of tab-lets prepared by direct compression of such powder with respect to, e.g., tablet weight variation. Flowability can be measured by Angle of Repose, Carr index, Hausner ratio, a visual inspection of the flow pattern (funnel or mass flow, etc.), flowability tester by use of different hole size (Ph. Eur method), or by evaluation of the tabletting process by measuring of tablet weight variation according to pharmacopea standard (e.g., European Pharmacopea). In a particular embodiment, the mixture of the present invention has flowability as assessed by visual inspection, which is suitable for the manufacture of tablets with an acceptable weight variation. In one embodiment, the mixtures of the present invention have a flowability which gives rise to a RSD for the tablet weight equal to or less than 5% (Ph. Eur. limit for tablets below 250 mg) or even equal to or less than 2%. RSD is Relative Standard Deviation, calculated as

$$\frac{\sqrt{\frac{\sum_{i=1}^{n}(Y_i-M)^2}{n-1}}}{\mu} \times 100\%$$

wherein (in this context) Y_i is the weight of a sample number i, μ is the mean of all samples drawn, and n is the number of samples drawn.

In the present context, mixing properties is understood to be the ability of a mixture to obtain homogeneity during processing. Mixing property is of importance as it impacts thequality *of* the final product, e.g. a tablet, obtained by processing, e.g. compressing the mixture. Mixing properties are typically assessed by determining the uniformity *of* the final product, e.g a tablet, and this is typically done by HPLC. In a particular

embodiment, the mixing properties of the mixtures of the present invention as determined by uniformity of content of the final product is RSD equal to or less than 6 % (USP limits for RSD); RSD between 2 % and 4%; or RSD equal to or less than 2 %.

In another embodiment, the invention relates to a process for making a pharmaceutical composition *of* the present invention, the process comprising the steps of shaping the mixture of the present invention into the desired form. In particular, the process comprises the steps of mixing the potassium salt of 5-[4-(3-Methyl-4-oxo-3,4-dihydro-qumazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione, α-lactose monohydrate and silicified microcrystalline cellulose (2% SiO_2) for a time sufficient to obtain a desired homogeneity, where after the glidants, magnesium stearate and talc are admixed, and the resulting mixture is compressed into tablets on a tabletting machine, e.g., a rotary tabletting machine. If desired, the tablets can be further film coated, e.g., with a suitable standard HPMC film coating.

For convenience, the potassium salt of 5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione will be referred to as "active compound".

The invention is further illustrated by reference to the following examples, none of which should be understood as limiting.

Example 1.

Component	Amount
Active compound	32.85 mg (corresponding to 9.963 %)
Lactose	194.01 mg (corresponding to 58.79 %)
Silicified microcrystalline cellulose	95.7 mg (corresponding to 29 %)
Magnesium stearate	2.475 mg(corresponding to 0.75 %)
Talc	4.95 mg (corresponding to 1.5 %)

The active compound was mixed with the fillers, silicified microcrystalline cellulose and lactose for an appropriated time until homogeneity was obtained. The glidents and lubricants, talc and magnesium stearate were admixed. The mixture was compressed into tablets with a given total mass of either 110 mg, 220 mg and 330 mg giving tablet strengths of 10 mg, 20 mg and 30 mg. The tablets can be film-coated with a standard HPMC film coating solution.

The lactose used was agglomerated α-lactose monohydrate with <63 μm NMT 6%, and the silicified microcrystalline cellulose used contained 2% colloidal silicon dioxide and had a mean particle size of 90 μm.

Example 2

Component	Amount
Active compound	10.95 mg (corresponding to 9.963 %)
Lactose	48.17 mg (corresponding to 43.78 %)
Silicified rnicrocrystalline cellulose	48.4 mg (corresponding to 44 %)
Magnesium stearate	0.825 mg (corresponding to 0.75 %)
Talc	1.65 mg (corresponding to 1.5 %)

The active compound was mixed with the fillers, silicified microcrystalline cellulose and lactose for an appropriated time until homogeneity was obtained. The glidents and lubricants, talc and magnesium stearate were admixed. The mixture was compressed into tablets with a given total mass of either 110 mg, 220 mg and 330 mg giving tablet strengths of 10 mg, 20 mg and 30 mg. The tablets can be film-coated with a standard HPMC film coating solution. The lactose used was agglomerated α-lactose monohydrate with <63 μm NMT 6%, and the silicified microcrystalline cellulose used contained 2% colloidal silicon dioxide and had a mean particle size of 90 μm.

Example 3

Component	Amount
Active compound	10.95 mg (corresponding to 9.963 %)
Lactose	74.57 mg (corresponding to 67.79 %)
Silicified microcrystalline cellulose	22 mg (corresponding to 20 %)
Magnesium stearate	0.825 mg (corresponding to 015 %)
Talc	1.65 mg (corresponding to 1.5 %)

The active compound was mixed with the fillers, silicified microcrystalline cellulose and lactose for an appropriated time until homogeneity was obtained. The glidents and lubricants, talc and magnesium stearate were admixed. The mixture was compressed into tablets with a given total mass of 110mg, 220 mg and 330 mg giving tablet strengths of 10 mg, 20 mg and 30 mg. The tablets can be film-coated with a standard HPMC filmcoating solution. The lactose used was agglomerated a-lactose monohydrate with <63 μm NMT 6%, and the silicified microcrystalline cellulose used contained 2% colloidal silicon dioxide and had a mean particle size of 90 μm.

Example 4

Component	Amount
Active compound	32.87 mg (corresponding to 10.27 %)
Lactose	207.13 mg (corresponding to 64.72 %)
Microcrystalline cellulose	64.0 mg (corresponding to 20 %)
Magnesium stearate	0.6 mg (corresponding to 0.5 %)
Talc	14.4 mg (corresponding to **4.5** %)

The active compound was mixed with the fillers, microcrystalline cellulose and lactose for an appropriated time until homogeneity was obtained. The glidents and lubricants, talc and magnesium stearate were admixed. Visual inspection of the mixture showed that manufacturing of tablets with acceptable weight variation was not possible as the flowability of the powder mixture was very poor. Furthermore adhesion to tablet punches was observed. Therefore, it was not possible to obtain data for flowability and mixing properties for the pre-sent mixture. The lactose use was anhydrous lactose (80% β-lactose), and the microcrystalline cellulose used was <250 μm NMT 8%.

Example 5

Component	Amount
Active compound	10.95 mg (corresponding to 5.48 %)
Lactose	110 mg (corresponding to 55 %)
Corn starch	35 mg (corresponding to 17 5 %)
Carboxymethyl cellulose sodium	44 mg (corresponding to 22 %)
Magnesium stearate	1 mg (corresponding to 0.5 %)

The active compound was mixed with corn starch, carboxymethyl cellulose sodium and lactose for an appropriated time until homogeneity was obtained. The lubricant, magnesium stearate was admixed. Visual inspection of the mixture showed that manufacturing of tablets with acceptable weight variation was not possible as the flowability of the powder mixture was very poor. Tablets could only be made by manual compression. Therefore, it was not possible to obtain data for flowability and mixing properties for the present mixture. The lactose used was a-lactose mono hydrate with <63 μm NMT 78%.

Example 6

Active compound	10.95 mg (corresponding to 5.48 %)
Calcium Phosphate	90 mg (corresponding to 45 %)
Lactose	50 mg (corresponding to 25 %)
Corn starch	45 mg (corresponding to 22.5 %)
Polyvinyl pyrrolidone	3.5 mg (corresponding to 1.75 %)
Magnesium stearate	1.5 mg (corresponding to 0 75 %)

The active compound was mixed with cornstarch, calcium phosphate, polyvinyl pyrrolidone and lactose for an appropriated time until homogeneity was obtained. The lubricant, magnesium stearate is admixed. Visual inspection of the mixture showed that manufacturing of tablets with acceptable weight variation was not possible as the flowability of the powder mixture was very poor. Tablets could only be made by manual compression. Therefore, it was not possible to obtain data for flowability and mixing properties for the present mixture. The lactose used was α-lactose mono hydrate with <63 μm NMT 78%.

Table 1 shows data on flowability and mixing properties of the mixtures of examples 1-6. The data are based on 3 x 10 measurements.

Example No		Tablet weight deviation (RSD) (Flowability)	Uniformity of content (RSD) (Mixing property)
1	10 mg	0.52%	1.59%
	30 mg	0.80%	1.77%
2	10 mg	1.01 %	1.27%
	30 mg	1.74%	2.41 %
3	10 mg	0.60%	2.11 %
	30 mg	0.75%	1.55%
4		Could not be analysed Very poor	Could not be analysed Very poor
5		Could not be analysed Very poor	Could not be analysed Very poor
6		Could not be analysed Very poor	Could not be analysed Very poor

The data for examples 1-3 show that the mixtures of the present invention have excellent flowability and mixing properties, and that it is possible to prepare tablets from these mixtures by direct compression. In contrast, the mixtures of examples 4-6 all have poor flowability and mixing properties, and it was not possible to prepare tablets by direct compression from these mixtures.

We claim:

1. A solid pharmaceutical composition comprising:

a) 5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy) benzyl]-thiazolidine-2,4-dione and/or pharmaceutically acceptable salt thereof present in the amount of from about 3.1% to about 15%;

b) lactose present in the amount of from about 44% to about 88%;

c) silicified microcrystalline cellulose present in the amount of from about 5% to about 44%;

d) magnesium stearate present in the amount of from about 0,5% to about 2%; and

e) talc present in the amount of from about 0,5% to about 2%.

2. The composition according to claim 1, wherein said 5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof is present in the amount of from about 8% to about 11%.

3. The composition according to claim 1, wherein said lactose is present in the amount of from about 60% to about 70%.

4. The composition according to claim 1, wherein said silicified microcrystalline cellulose is present in the amount of from about 15% to about 25%.

5. The composition according to claim 1, wherein said magnesium stearate is present in the amount of from about 0.5% to about 1%.

6. The composition according to claim 1, wherein said talc is present in the amount of from about 1% to about 2%.

7. The composition according to claim 1, which is a tablet.

8. The composition according to claim 1, wherein said lactose is α-lactose monohydrate.

9. The composition according to claim 1, wherein said silicified microcrystalline cellulose comprises 2% silicon dioxide.

10. The composition according to claim 1, wherein 5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione is present as its potassium salt.

11. The composition of claim 1, which is a tablet with the following content:

5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione, potassium salt	9 96 %
α-lactose monohydrate	67.79%
Silicified microcrystalline cellulose (2% SiO_2)	20.0%
Magnesium stearate	0.75%
Talc	1.5%.

12. A mixture comprising 5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione or pharmaceutically acceptable salt thereof present in the amount of from about 3.1% to about 15%; lactose present in the amount of from about 44% to about 88%; silicified microcrystalline cellulose present in the amount of from about 5% to about 44%; magnesium stearate present in the amount of from about 0,5% to about 2%; and talc present in the amount of from about 0,5% to about 2%.

13. The mixture according to claim 12, wherein said 5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione or a pharmaceutically accept-able salt thereof is present in the amount of from about 8% to about 11%.

14. The mixture according to claim 12, wherein said lactose is present in the amount of from about 60% to about 70%.

15. The mixture according to claim 12, wherein said silicified microcrystalline cellulose is present in the amount of from about 15% to about 25%.

16. The mixture according to claim 12, wherein magnesium stearate is present in the amount of from about 0.5% to about 1%.

17. The mixture according to claim 12, wherein said talc is present in the amount of from about 1% to about 2%.

18. The mixture according to claim 12, which is a tablet.

19. The mixture according to claim 12, wherein said lactose is α-lactose monohydrate.

20. The mixture according to claim 12, wherein said silicified microcrystalline cellulose comprises 2% silicon dioxide.

21. The mixture according to claim 12, wherein 5-[4-(3-Methyl-4-oxo-3,4-dihydroqunazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-drone is present as its potassium salt.

22. The mixture of claim 12, which has the following content:

5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione, potassium salt	9 96 %
α-lactose monohydrate	67.79%
Silicified microcrystalline cellulose (2% SiO_2)	20.0%
Magnesium stearate	0.75%
Talc	1.5%.

23. A process for the manufacture of a pharmaceutical composition comprising the step of forming the mixture according to claim 12.

24. A process for the manufacture of a pharmaceutical composition comprising the step of forming the mixture according to claim 22.

25. The process of claim 23, which comprises

i) mixing from about 3.1% to about 15% of 5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione or its salt, from about 44% to about 88% of lactose, and from about 5% to about 44% of silicified microcrystalline cellulose to a desired homogeneity;

ii) admixing from about 0,5% to about 2% of magnesium stearate and from about 0,5% to about 2% of talc; and

iii) compressing the resulting admixture into a tablet.

26. The process of claim 25, further comprising film coating said tablet.

27. The process of claim 25, wherein the following amounts of specified components are used to form the admixture:

5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione, potassium salt	9 96 %
α-lactose monohydrate	67.79%
Silicified microcrystalline cellulose (2% SiO_2)	20.0%
Magnesium stearate	0.75%
Talc	1.5%

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(54) Title: A PHARMACEUTICAL FORMULATION OF BALAGLITAZONE

(57) Abstract: A formulation of 5-[4-(3-Methyl-4-oxo-3,4-dihydro-quinazolin-2-ylmethoxy)-benzyl]-thiazolidine-2,4-dione and/or pharmaceutically acceptable salts thereof is provided.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) : A01 N 43/24; A61K 31/445,9/14
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/32191 (WEIBEL et al) 8 June 2000 (08.06.2000), pages 1-10	1-27
Y	US 5,585,115 (SHERWOOD et al) 17 December 1996 (17.12.1996), abstract.	9, 20

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